

Interferon alfa- 2



Brand Name: Roferon-A (2a), Intron A (2b)

Drug Class: Opportunistic Infection and Other Drugs

Drug Description

The interferon alfa family comprises a number of highly homologous, species-specific proteins and glycoproteins. [1] Naturally occurring interferon alfa is a protein with antiviral, antiproliferative, and immunomodulating activity. Interferons alfa-2a and alfa-2b are of recombinant DNA origin and exist as single interferon subtype preparations. They are commercially available as peginterferons alfa-2a and alfa-2b, which contain the drugs covalently bound to polyethylene glycol (PEG) monomethoxy ether. [2]

Interferon alfa-2a and alfa-2b are synthetic interferons manufactured by recombinant DNA technology using a genetically engineered *Escherichia coli* bacterium. [3] [4] Interferons alfa-2a and alfa-2b are biosynthetic forms of interferon alfa that consist of 165 amino acids. Interferons alfa-2a and alfa-2b differ at amino acid position 23; alfa-2a has a lysine in that position, while alfa-2b has an arginine at that position. Compared to other interferon alfa subtypes, interferons alfa-2a and alfa-2b both have a deletion at position 44 in the amino acid sequence. [5]

Interferon alfa-2b is commonly prescribed in a kit with ribavirin. [6]

HIV/AIDS-Related Uses

Interferon alfa-2 is used in the treatment of certain viral infections, including chronic hepatitis B, hepatitis C, and hepatitis D infections; acute hepatitis C infection; and infections caused by human papillomavirus. These diseases, especially hepatitis, are especially prevalent in individuals with HIV/AIDS.[7] Interferons alfa-2a and alfa-2b were approved by the FDA on November 21, 1988 [8] , and are indicated for the treatment of AIDS-associated Kaposi's sarcoma in adults.[9]

Non-HIV/AIDS-Related Uses

Interferon alfa is used in the treatment of chronic hepatitis B and C virus infections; acute hepatitis C infection; postexposure prophylaxis following occupational exposure to hepatitis C virus; chronic

hepatitis D infection, non-A, non-B/C hepatitis in adults with compensated liver disease who have a history of blood or blood product exposure or are hepatitis C virus (HCV) antibody positive; human papillomavirus infections; West Nile virus infection [10] ; hairy cell leukemia; AIDS-related Kaposi's sarcoma; chronic myelogenous leukemia; non-Hodgkin and cutaneous T-cell lymphomas; renal cell carcinoma; bladder, ovarian, and cervical cancers; basal cell carcinoma; metastatic melanoma; multiple myeloma; various angiomatous (angiogenic) disorders; and metastatic small intestinal carcinoid tumors.[11]

Interferon alfa-2b is additionally indicated for treatment of condyloma acuminatum (genital warts) and mycosis fungoides.[12]

Pharmacology

Although the precise mechanisms of antiviral activity of interferon alfa have not been fully elucidated, interferons with antiviral activity appear to bind to specific membrane receptors on cell surfaces and initiate a complex sequence of intracellular events, including induction of certain enzymes, suppression of cell proliferation, various immunomodulating activities, and inhibition of viral replication in virus-infected cells.[13] Antiviral and antiproliferative actions are thought to be related to alterations in the synthesis of RNA, DNA, and cellular proteins, including oncogenes. The exact mechanism of antineoplastic activity is unknown but could be related to interferon alfa's antiviral (inhibiting virus replication in virus-infected cells), antiproliferative (suppressing cell proliferation), and immunomodulatory (enhancing phagocytic activity of macrophages and augmenting specific cytotoxicity of lymphocytes for target cells) effects.[14] Because of their relative species-specific activity, interferons intended for human use are of human origin (e.g., prepared using donor-provided human cells such as leukocytes, using cultured human cell lines such as lymphoblastoid cells, or using recombinant techniques that employ human genes).[15]

The importance, if any, of the single amino acid difference between interferons alfa-2a and -2b has

Interferon alfa- 2

Pharmacology (cont.)

not yet been established. While both the amino and carboxy terminal regions of the molecules may be involved in eliciting antiviral activity, studies to determine which regions of the molecules confer various degrees of activity have yielded conflicting results. Some evidence indicates that different regions may be involved in eliciting various activities of the drug.[16]

Absorption of interferons alfa-2a and alfa-2b is high (greater than 80%) when administered intramuscularly or subcutaneously. When given intralesionally, plasma concentrations of interferons alfa-2 are below detectable levels, but systemic effects have been reported, indicating some systemic absorption.[17] For systemic effects, interferon alfa is administered parenterally because the drug is susceptible to degradation by proteolytic enzymes of the gastrointestinal tract. Interferon alfa-2 is well absorbed following intramuscular (IM) or subcutaneous (SC) injection. Peak serum interferon alfa-2 concentrations following IV administration of the drug generally occur within 15 to 60 minutes and are substantially greater than those attained after IM or SC administration. However, serum interferon alfa concentrations following IM or SC administration are generally maintained longer than those produced by rapid injection or rapid (e.g., 40 minutes or less) IV infusion. Depending on the dose, serum interferon concentrations generally are detectable for approximately 4 hours to 8 hours after rapid IV injection or infusion or for approximately 16 hours to 30 hours after IM or SC injection.[18] Time to peak concentration is 3.8 hours for a single IM dose of interferon alfa-2a, and 7.3 hours for an SC dose.[19] Time to peak concentration of a single IM or SC dose of interferon alfa-2b is usually 3 hours to 12 hours.[20]

Limited data suggest that mixtures of naturally occurring human or animal interferons are widely and rapidly distributed into body tissues after parenteral administration, with the highest concentrations occurring in spleen, kidney, liver, and lung. Limited evidence also indicates interferon uptake and/or binding by other kinds of tissue or tumors. Although a similar pattern of tissue distribution was noted in animals given certain

recombinant DNA-derived interferons (human interferon alfa-2c), animal studies in which recombinant interferon alfa-2a or alfa-2b were used suggest that these interferons are not concentrated in any organ or that only the kidney, which appears to be the principal site of interferon metabolism, demonstrates substantial uptake of the drugs. The volume of distribution of interferon alfa in humans reportedly approximates 20% to 60% of body weight. Interferon alfa does not readily distribute into cerebrospinal fluid (CSF) following systemic administration of mixtures of naturally occurring human or recombinant interferons in animals or humans, although low concentrations have been detected in CSF following administration of large systemic doses. It is not known whether interferon crosses the placenta or is distributed into breast milk in humans, but studies in mice indicate that murine interferon is distributed into milk.[21]

Both interferons alfa-2a and alfa-2b are in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. For interferon alfa-2a, studies in rhesus monkeys at doses approximately 20 to 500 times the therapeutic human dose found a significant increase in abortifacient activity but no evidence of teratogenic activity. For interferon alfa-2b, studies in rhesus monkeys at doses of 90 to 180 times the IM or SC dose of 2 million IUs per square meter of body surface area found an abortifacient effect. When given in high doses via daily IM injection in rhesus monkeys, interferon alfa has been shown to cause menstrual cycle changes, with normal menstrual rhythm returning after interferon alfa was withdrawn. Use of recombinant interferon alfa-2a has been associated with reversible menstrual irregularities, including prolonged or shortened menstrual period and erratic bleeding with anovulation in rhesus monkeys given 5 million and 25 million IUs per kg of body weight per day. It is not known if interferon alfa distributes into milk in humans; mouse interferons do distribute into mouse milk. Avoidance of breastfeeding in nursing mothers should be considered while alpha interferon is being administered because of the potential of serious adverse effects in nursing infants.[22]

Interferon alfa-2/ribavirin combination therapy is in FDA Pregnancy Category X. Significant

Interferon alfa- 2

Pharmacology (cont.)

teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Use of interferon alfa with ribavirin is contraindicated in women who are pregnant or in the male partners of women who are pregnant. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.[23]

Elimination of interferon alfa is rapid from plasma following IV injection or IV infusion in animals or humans, while more prolonged concentrations are observed following IM or SC administration. In healthy individuals with normal renal function, plasma concentrations of interferon alfa appear to decline in a biphasic manner. Limited data from studies in humans receiving interferon alfa-2a or alfa-2b suggest that variability in the reported elimination half-life of interferon alfa may be related to route or method of administration, interindividual variability in drug disposition, and/or presence of disease.[24] The IM half-life of interferon alfa-2a is 6 hours to 8 hours; the half-life for IV infusion is 3.7 hours to 8.5 hours (mean 5.1 hours). The IV or SC half-life of interferon alfa-2b is 2 hours to 3 hours.[25]

Tumor cells may be resistant to the antiproliferative effects of interferon alfa despite the presence of functional, specific high-affinity interferon receptors on their cell surfaces. Resistance to the antiproliferative effects of interferon alfa usually occurs at the cellular level; however, the precise mechanism responsible for resistance to the drugs may differ among cell populations. An association has been observed between the presence of neutralizing anti-interferon antibody and clinical resistance to interferon alfa in some patients with hairy cell leukemia, suggesting that resistance may not always arise at the intracellular level. However, a causal relationship between the presence of antibodies and disease progression and/or resistance to interferon alfa therapy was not established, and some patients who developed neutralizing antibodies to interferon continued to respond to the drug. Therefore, the development of antibodies should not necessarily be interpreted as an indication of drug resistance.[26]

Adverse Events/Toxicity

Because interferon alfa-2 is used for many different conditions and in many different doses, the actual frequency of side effects may vary.[27]

Interferon alfa-2 may cause serious adverse effects such as anemia; autoimmune diseases, including vasculitis, arthritis, hemolytic anemia, and erythematous syndrome; cardiotoxicity; hepatotoxicity; hyperthyroidism or hypothyroidism; transient ischemic attacks; leukopenia; neurotoxicity; peripheral neuropathy; and thrombocytopenia. Some lesser side effects that may not need medical attention include blurred vision, change in taste or metallic taste, cold sores or stomatitis, diarrhea, dizziness, dry mouth, dry skin or itching, flu-like syndrome, increased sweating, leg cramps, loss of appetite, nausea or vomiting, skin rash, unusual tiredness, weight loss, and partial loss of hair.[28]

Drug and Food Interactions

Concomitant administration of interferon alfa-2 with zidovudine can increase the risk of hematologic (e.g., neutropenia, thrombocytopenia) and hepatic toxicity. The increased risk of such toxicity may be synergistic, although the mechanism of such potential synergy is not known. Concomitant therapy with interferon alfa and vidarabine may potentiate the neurotoxicity of vidarabine.

Interferon alfa-2 should be used with caution in patients receiving drugs that are potentially myelosuppressive. The antineoplastic activity of interferon alfa and certain cytotoxic agents (e.g., cisplatin, cyclophosphamide, doxorubicin, eflornithine, fluorouracil, mechlorethamine, melphalan, methotrexate, mitomycin, nitrosureas, vinblastine, vincristine) may be additive or synergistic in vitro and in vivo against some tumors. Further studies are needed to determine the potential interactions between interferon alfa and antineoplastic agents, and to establish the optimum regimens, including dosages and sequencing. Limited data indicate that the antineoplastic activity of interferon alfa and vinblastine does not appear to be additive against renal cell carcinoma or AIDS-related Kaposi's sarcoma. However,

Interferon alfa- 2

Drug and Food Interactions (cont.)

vinblastine may potentiate the toxicity of interferon alfa when these drugs are used concomitantly. Neurotoxicity (e.g., paresthesia, peripheral neuropathy) in patients receiving interferon alfa usually occurs more frequently in those who have previously received or are concomitantly receiving vinca alkaloids (e.g., vinblastine, vincristine).

Response rates in patients with AIDS-related Kaposi's sarcoma receiving combination chemotherapy with interferon alfa and etoposide suggest that the combination has no synergistic antineoplastic activity against this malignancy, and the incidence of toxicity (e.g., hematologic effects) is higher with the combination than with either drug alone. Combination therapy of high-dose aldesleukin with antineoplastic agents, specifically interferon alfa, have caused hypersensitivity reactions consisting of erythema, pruritus, and hypotension. Aldesleukin in combination with interferon alfa-2 has been associated with the development or exacerbation of autoimmune disease and inflammatory disorders.

Interferon alfa-2 has been reported to reduce the clearance of theophylline, possibly via the hepatic cytochrome P450 enzyme system. It is not known whether interferon alfa itself interacts with cytochrome P450 enzymes or if the drug exerts this effect through an interaction with the immune system. Interferon alfa may also inhibit metabolism of barbiturates. Further studies and experience are needed to establish the clinical importance of this potential drug interaction and to determine whether interferon alfa interacts with other drugs that are metabolized by the hepatic cytochrome P450 enzyme system.

It has been reported that interferon alfa-2 also inhibits the metabolism of antipyrine.

Interferon alfa-2 has been used as an adjunct to radiation therapy in patients with various neoplasms; however, severe toxicity has been reported in some patients receiving such combined therapy. Patients receiving interferon alfa with radiation therapy should be closely monitored.[29]

Contraindications

Alpha interferons, including interferons alfa-2a and alfa-2b, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistent severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping interferon therapy.[30]

Interferon alfa-2 is contraindicated in patients hypersensitive to interferon alfa or any component of the product formulations. Combination therapy with ribavirin is contraindicated in women who are pregnant or in men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of patients taking combination interferon alfa/ribavirin therapy.[31]

Risk-benefit should be considered if patients have a history of autoimmune disease; severe cardiac disease, including recent myocardial infarction; diabetes mellitus (if the patient is prone to ketoacidosis), ischemic disorders, or pulmonary disease; existing or recent chicken pox, including recent exposure or herpes zoster; compromised CNS function, severe or history of psychiatric or seizure disorders; infectious disorders that interferon alfa may aggravate or cause fatal or life-threatening effects; or thyroid function impairment.[32]

Clinical Trials

For information on clinical trials that involve Interferon alfa-2, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Interferon alfa-2 AND HIV Infections.

Dosing Information

Mode of Delivery: Interferon alfa-2a: intramuscular, intravenous, and subcutaneous.[33] [34]

Interferon alfa-2b: intralesional, intramuscular, intravenous, and subcutaneous.[35] [36]

Interferon alfa- 2



Dosing Information (cont.)

Dosage Form: Interferon alfa-2a:

Single use injectable solution (subcutaneous or intramuscular administration): 36 million IU in 1-ml vials.[37]

Single use prefilled syringes (subcutaneous administration only): 3, 6, and 9 million IU in 0.5-ml vials.[38]

Multidose injectable solution (subcutaneous or intramuscular administration): 18 million IU in 1-ml vials.[39]

Interferon alfa-2b:

Powder for reconstitution with diluent, for injection: 5 million IU in 1-ml vials, 10 million IU in 2-ml vials, 18 million IU in 1-ml vials, 25 million IU in 5-ml vials, and 50 million IU in 1-ml vials.[40]

Solution for injection: 3, 5, and 10 million IU single dose vials; 18 million IU and 25 million IU multidose vials.[41]

Multidose injection pens (subcutaneous only): 6 doses of 3 million IU in a single pen; 6 doses of 10 million IU in a single pen.[42]

Multidose injectable solution: 6 3-million IU vials; 6 5-million IU vials; 6 10-million IU vials.[43]

Available packaged in a kit with ribavirin.[44]

Storage: Interferons alfa-2a and alfa-2b should be stored between 2 C and 8 C (36 F to 46 F) unless otherwise specified by the manufacturer; protect from freezing.[45]

Interferon alfa-2a injectable solution and prefilled syringes should not be frozen or shaken.[46]

When dispensing for self-administration by the patient, physicians should make sure that patient instructions are included and that the patient understands how to prepare and administer the injections, including proper use of disposable syringes.[47]

Chemistry

CAS Name: Interferon alfa-2a[48]

Interferon alfa-2b[49]

CAS Number: 779007-69-8 (2a)[50]

99210-65-8 (2b)[51]

Molecular formula: C860-H1353-N227-O255-S9 (2a) ; C860-H1353-N229-O255-S9 (2b)[52]

Molecular weight: approximately 19 kDa[53]

Physical Description: Solutions of interferon alfa-2a are clear.[54]

Solutions of interferon alfa-2b are clear and colorless to light yellow.[55]

Stability: Reconstituted solutions of interferon alfa-2a for injection should be used within 30 days and stored between 2 C to 8 C (36 F to 46 F).[56] When stored as directed, the commercially available injection has an expiration date of 12 months following the date of manufacture. Exposure of the injection to room temperature should not exceed 24 hours.[57]

Interferon alfa-2b for intravenous administration should be prepared by mixing with 0.9% sodium chloride immediately prior to use. Interferon alfa-2b powder for injection is stable up to a temperature of 45 C (113 F) for up to 7 days. The reconstituted solution with bacteriostatic diluent is stable for 1 month between 2 C to 8 C (36 F to 46 F); when prepared with sterile water for injection, solutions are stable for 24 hours when stored between 2 C to 8 C (36 F to 46 F).[58] [59] When stored as directed, the commercially available powder for injection has an expiration date of 24 months following the date of manufacture. Any remaining reconstituted solution should be discarded after the period noted previously. When refrigeration is unavailable (e.g., while traveling), interferon alfa-2b powder and reconstituted solutions are stable for short periods (1 to 2 days) at ambient temperatures up to 104 F. However, for longer periods without refrigeration, vials should be placed in a suitable container (e.g., plastic bag) and

Interferon alfa- 2



Chemistry (cont.)

kept cold (2 C to 8 C; 36 F to 46 F) in a cooler or thermos. Interferon alfa-2b is stable over a pH range of 6.5 to 8.[60]

Other Names

Recombinant Interferon Alfa-2a[61]

Recombinant Interferon alpha-2a[62]

Recombinant Interferon Alfa-2b[63]

Recombinant Interferon alpha-2b[64]

IFN[65]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

Interferon alfa- 2



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Interferon alfa- 2



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Interferon alfa- 2



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